MERETEK

The Breath Test Company

March 1, 2000 2447 '00 MAR -2 A9:47

By Federal Express

US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Dockets Management Branch [HFA-305]
5630 Fishers Lane [Room 1061]
Rockville, MD 20852

Attention: Dr. Mehul Mehta at FDA / CDER
FAX: 301-480-3212
Dr. David Green at FDA / CBER
FAX: 301-827-5394

RE: Call for Comments on DRAFT GUIDANCE for Industry

DOCKET Number: 99D-5047 DATED November, 1999

Comments on:

Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling

Dear Drs. Mehta and Green:

Our comment on this Draft Guidance for Industry, Pharmacokinetics in Patients With Impaired Hepatic Function, is strong agreement with the need to define and incorporate such assessments of hepatic function in the study of new therapeutic entities. Further, hepatic function assessment and monitoring, while critical in the target patient populations who also exhibit hepatic impairment, has valuable application in other study patients or volunteers as well.

The Guidance is primarily directed to addressing study design. However, our most specific comment is not in the study design, per se, but on the recommendations of how actual hepatic capacity may be assessed prior to and through study [and ultimately, on treatment].

Five general clinical or reported methods of assessing liver function are listed in the appendix to this Draft Guidance. These are not all commercially established methods for determining liver function. Therefore, we request inclusion of a sixth method which has published history[1-10].

99D-5047 C10

Corporate Offices and Breath Test Center 618 Grassmere Park Drive Suite 20 Nashville, Tennessee 37211 Phone 615•333•6336 Fax 615•333•6202
Breath Test Center and Research Laboratory Medical Towers Building 1709 Dryden Road Suite 1513 Houston, Texas 77030 Phone 713•799•1282 Fax 713•799•8395

The hepatic P450 mixed function oxidase is a significant pathway for the oxidative disposition of drugs and other xenobiotics. Impairment of this functional capacity significantly prolongs the residence time of administered drugs and is a well-documented measure of liver disease. This capacity can be estimated from the oxidation of ^{13}C-dimethylaminoantipyrine in a Breath Test.

We suggest the inclusion of this Meretek Aminopyrine Breath Test, a non-invasive, non-radioactive breath test as a means for classification of liver impairment. The values obtained in prior clinical investigation show strong correlation with the Child-Pugh scores and range from a cumulative percent dose oxidation value in 2h of 10% in normal subjects to as low as 1% in near-terminal liver cirrhotics.[1-6] Animal and human studies have shown that the aminopyrine breath test measures the active hepatocyte mass of the liver, a functional measurement not provided by other commonly used tests.[7-8]

Because this breath test detects the effects of drug binding to the P450 system, it has an equally valuable screening function for proposed new drugs in normal subjects and we suggest that it be noted for use in this manner before and during drug administration. This diagnostic has the potential to forecast prolongation of other concurrently administered medications, such as anticoagulant therapy, as well [9-10].

The Investigational diagnostic use of ^{13}C-aminopyrine for the assessment of hepatic function was begun under FDA review in 1972. FDA requested applications with intent for commercialization and these are under preparation for submission by Meretek Diagnostics, Inc. The non-invasive test as designed requires the collection of a baseline breath sample, the ingestion of a solution containing 500 mg ^{13}C-aminopyrine and the collection of timed post- dose breath samples.

Breath analysis by gas isotope ratio mass of the increase in $^{13}CO_2$ from an administered substrate is a diagnostic technique already commercially available (for the detection and monitoring of active *Helicobacter pylori*, Meretek UBT®).

Should there be any questions or additional information needed, please contact me by phone **713-799-1282**; fax **713-799-8395**; or e-mail **pkleinbcm.tmc.edu**.

Thank you for consideration of this comment.

Sincerely,

Peter D Klein

Meretek Diagnostics, Inc.

Dr. Peter Klein
Vice President, Research and Development

Duagnostic ability of aminopyrine breath test

1. Beuers U, Jager F, Wahllander A, Ansari H, Kirsch CM. Prognostic value of the intravenous 14C-aminopyrine breath test compared to the Child-Pugh score and serum bile acids in 84 cirrhotic patients. Digestion 1991; 50:212-218.

2. Gill RA, Goodman MW, Golfus GR, Onstad GR, Bubrick MP. Aminopyrine breath test predicts surgical risk for patients with liver disease. Ann Surg 1983; 198:701-704.

3. Henry DA, Kitchingman G, Langman MJ. [14C]Aminopyrine breath analysis and conventional biochemical tests as predictors of survival in cirrhosis. Dig Dis Sci 1985; 30:813-818.

4. Monroe PS, Baker AL, Schneider JF, Krager PS, Klein PD, Schoeller D. The aminopyrine breath test and serum bile acids reflect histologic severity in chronic hepatitis. Hepatology 1982; 2:317-322.

5. Saunders JB, Lewis KO, Paton A. Early diagnosis of alcoholic cirrhosis by the aminopyrine breath. Gastroenterology 1980; 79:112-114.

6. Schneider JF, Baker AL, Haines NW, Hatfield G, Boyer JL. Aminopyrine N-demethylation: a prognostic test of liver function in patients with alcoholic liver disease. Gastroenterology 1980; 79:1145-1150.

Correlation of aminopyrine breath test with active hepatocyte mass

7. Lauterburg, BH, Bircher J. Expiratory measurement of maximal aminopyrine demethylation : in vivo effect of phenobarbital, partial hepatectomy, portacaval shunt, and bile duct ligation in the rat. J Pharmaco[Exp Ther 1976; 296: 501-505.

8. Hepner GW, Vesell ES. Assessment of aminopyrine metabolism in man by breath analysis after oral administration of ^{14}C aminopyrine. Effects of phenobarbital, disulfram and portal cirrhosis N Engl J Med 1974; 291:1384-1388

Aminopyrine breath test detection of drug effects on liver function

9. Rollinghoff W, Paumgartner G. Inhibition of drug metabolism by cimetidine in man: dependence on pretreatment microsomal liver function. Eur J Clin Invest 1982; 12:429-43

10. Kramer, P, McClain, CJ. Depression of aminopyrine metabolism by influenza vaccination. N Engl J Med 1981; 205:1262-1264

Federal Express

SHIP DATE: 01MAR00
ACC# 189767013

MERETEK DIAGNOSTICS INC
618 GRASSMERE PARK DR STE 20
NASHVILLE TN 37211
(615)333-6336

ACTUAL WGT: 1 LBS MAN-WT

TO: US Dept of Health & Human Services (301)594-2567
FDA, Ctr for Drug Eval. & Research
Dockets Management Branch[HFA-305]
5630 Fishers Lane [Room 1061]
Rockville MD 20852

4317 4102 9292

FedEx.

REF:

PRIORITY OVERNIGHT THU

CAD# 0657015 01MAR00

Deliver by:
02MAR00

TRK# 4317 4102 9292 Form 0201

AA

IAD

20852 -MD-US XA EDGA

#153077077.SP G.T. 799

The World On Time®